

REMARKS

Applicants have amended claim 56 and canceled claims 72-75. Following entry of this amendment, claims 56, 69-71, 76 and 78 will be pending in this application.

Applicants have canceled claims 72-75 without prejudice or waiver of applicant's right to file for and obtain claims directed to any canceled subject matter in this application or in future divisional or continuing applications claiming priority from this application.

Applicants have amended claim 56 to specify that the BMP is selected from the group consisting of OP-1, OP-2, OP-3, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-15, Vgr-1, DPP, 60A, Vg1, CBMP2A, CBMP2B, GDF-1, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, MP121, DORSALIN, UNIVIN, NODAL, SCREW, ADMP and NURAL. Support for this amendment may be found, for example, at specification page 31, lines 14-22; page 33, line 27 to page 36, line 11; page 37, lines 4-23; page 39, lines 3-9; page 46, line 18 - page 52, line 3.

Applicants have also amended claim 56 to specify that the combination of ACE inhibitor and BMP morphogen is capable of

inducing a synergistic effect on reducing proteinuria level in a diabetic nephropathy model. Support for this amendment may be found, for example, at specification page 20, lines 13-16; and page 142, line 18 to page 143, line 14.

None of the amendments introduces any new matter.

THE REJECTIONS

Claim rejection under 35 USC 103(a)

Claims 56, 70-76 and 78

The Examiner has rejected claims 56, 70-76 and 78 under 35 U.S.C. 103(a) as being obvious over U.S. Patent 6,498,142 ("Sampath") in view of London et al., "Antihypertensive effects and arterial haemodynamic alterations during angiotensin converting enzyme inhibition", Journal of Hypertension, 14:1139-1146 (1996) ("London"). The Examiner alleges that the unexpected properties of the claimed combination are insufficient to rebut a prima facie case of obviousness and that applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent. Applicants traverse.

First, applicants have cancelled claims 72-75, thus

rendering the Examiner's rejection moot with respect to these claims.

Second, applicants submit that, contrary to the Examiner's allegations, Sampath and London do not teach or suggest the general expectation of a "greater than additive" effect for the combination of an ACE inhibitor and an BMP morphogen. The Examiner cites Ex parte The NutraSweet Co. in support for this proposition. 19 U.S.P.Q.2d 1586 (Bd. Pat. App. & Inter. 1991). In Ex Parte The NutraSweet Co., the court refers to specific teachings in the prior art that suggest a general expectation of "greater than additive" effects of sweeteners (Id. at 1588). In contrast, there are no specific teachings in either Sampath or London or from any other source that suggest a general expectation of greater than additive effect for the combination of ACE inhibitor and BMP morphogen. In fact, neither Sampath nor London suggest additive, let alone, synergistic effects of the combination.

Applicants further submit that there was no teaching, suggestion or motivation in the state of the prior art to combine the two references or to expect a "greater than additive" effect of the combination. As illustrated in the Hruska reference, which was published before the priority date of the application (Hruska et

al., "Osteogenic protein-1 prevents renal fibrogenesis associated with ureteral obstruction", Am. J. Physiol. Renal Physiol., 280:F130-F143, (2000) ("Hruska" of record)) the effect of enalapril or OP-1 on the treatment of renal injury was compared in a side-by-side analysis. OP-1 performed better or equal to enalapril in a number of assays (see, for example, Figures 3-11). Based on Hruska, one of skill in the art would not have been motivated to use enalapril and OP-1 together or expect that the combination would have a synergistic effect. If it were obvious that the combination would have a synergistic effect, one would have expected at least a suggestion of this in the reference. Therefore, one of ordinary skill in the art would have no reason to expect "greater than additive" effects of the combination of ACE inhibitors and BMP morphogens.

Finally, solely to expedite prosecution of this application, applicants have amended claim 56 (and therefore claims dependent therefrom) to recite that the combination of an ACE inhibitor with a BMP morphogen selected from a specific list of BMPs is capable of inducing a synergistic effect on reducing proteinuria levels in a diabetic nephropathy model. Accordingly, applicants respectfully request this rejection be withdrawn.

Claims 56 and 69

The Examiner has rejected claims 56 and 69 under 35 U.S.C. 103(a) as being obvious over the teaching of Sampath in view of London and further in view of Salvetti et al., "Newer ACE Inhibitors A Look at the Future", Drugs, 40:800-28 (1990) ("Salvetti").

As discussed above, applicants submit that nothing in Sampath, or London either alone or in combination, teaches or suggests the general expectation of "greater than additive" effects. Salvetti does not remedy this deficiency. Salvetti discloses ACE inhibitors and that enalapril is more potent than other ACE inhibitors and has a longer duration of action. Accordingly, applicants respectfully request this rejection be withdrawn.

Obviousness-type Double Patenting

U.S. Patent No. 6,677,432, London and Vukicevic
Claims 56, 71-76 and 78

The Examiner has rejected claims 56, 71-76 and 78 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of U.S. Patent No. 6,677,432 ("the '432 patent") in view of London and further in view of Vukicevic. Applicants traverse.

First, applicants have canceled claims 72-75, thus rendering the Examiner's rejection moot with respect to these claims.

Second, applicants have amended claim 56 (and therefore, claims dependent therefrom) to recite a pharmaceutical composition comprising an ACE inhibitor together with specific BMPs, wherein the combination is capable of inducing a synergistic effect on reducing proteinuria levels in a diabetic nephropathy model.

Contrary to the Examiner's assertion, the claims of the '432 patent do not recite OP-1 and/or other morphogens comprising the C-terminal seven cysteine domain. Rather, the claims of the '432 patent are directed to OP-1 mutants with specific amino acid residue substitutions in the C-terminal seven cysteine domain of that protein. And, as acknowledged by the Examiner, claims 1-13 of the '432 patent do not recite treatment of renal diseases. London discloses the administration of ACE inhibitors for acute renal failure associated with ischemia. Vukicevic discloses that OP-1 may be useful for treatment of acute renal failure.

The claims of the instant application do not recite OP-1 mutants. They recite specific BMPs. At best, a combination of the claims of the '432 patent with London and/or Vukicevic would be a

combination of the specific OP-1 mutants of the '432 patent with an ACE inhibitor. The claims of the instant application do not recite such a combination. As such, claims 1-13 of the '432 patent cannot form the basis for an obviousness-type double patenting rejection because the amended claims of the instant application are patentably distinct and do not define an invention that is merely an obvious variation of the invention claimed in the '432 patent.

Moreover, applicants submit that the synergistic effect on reducing proteinuria levels using the combination of an ACE inhibitor with specific BMPs, as recited in the amended claims of the instant application, is nowhere taught or suggested by claims 1-13 of the '432 patent, either alone or in combination with London and/or Vukicevic. Indeed, even if claims 1-13 of the '432 patent were combined with the teachings of London and/or Vukicevic, the skilled worker would have no reason to expect that the combination of the specifically recited BMPs with an ACE inhibitor would have a synergistic effect on reducing proteinuria levels. As such, claims of the instant application are not obvious over claims 1-13 of the '432 patent in view of London and/or Vukicevic.

Finally, applicants respectfully submit that the issuance of the amended claims of the instant application would not provide

an unjustified extension of the term of the right to exclude granted by the '432 patent.

For all the above reasons, applicants request that the Examiner withdraw this obviousness-type double patenting rejection.

U.S. Patent No. 6,846,906, London and Vukicevic
Claims 56, 71-76 and 78

The Examiner has rejected claims 56, 71-76 and 78 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-5 of U.S. Patent No. 6,846,906 ("the '906 patent") in view of London and further in view of Vukicevic. Applicants traverse.

First, applicants have canceled claims 72-75, thus rendering the Examiner's rejection moot with respect to these claims.

Second, with respect to the remaining claims, claims 1-5 of the '906 patent cannot form the basis for an obviousness-type double patenting rejection for the same reasons that claims 1-13 of the '432 patent cannot form the basis for an obviousness-type double patenting rejection.

More specifically, the claims of the '906 patent are directed to chimeric TGF- β superfamily proteins, wherein the finger 2 subdomain is from CDMP-2 and the finger 1 and heel subdomains are

from a different member of the superfamily. The claims of the '906 patent do not merely recite OP-1 and/or morphogens comprising the C-terminal seven cysteine domain, as suggested by the Examiner. And, as acknowledged by the Examiner, claims 1-5 of the '906 patent do not recite treatment of renal diseases.

The amended claims of the instant application recite specific BMPs, not chimeric proteins. The combination of claims 1-5 of the '906 patent with London and/or Vukicevic would yield a combination of a chimeric TGF- β superfamily protein with an ACE inhibitor. The amended claims of the instant application do not recite such a combination. Therefore, the amended claims of the instant application are patentably distinct from claims 1-5 of the '906 patent.

Moreover, the amended claims of the instant application recite a synergistic effect on reducing proteinuria levels using the combination of an ACE inhibitor with specific BMPs, which is nowhere taught or suggested by the claims of the '906 patent, either alone or in combination with London and/or Vukicevic. The skilled worker would have no reason to expect that the combination of the specifically recited BMPs with an ACE inhibitor would have a synergistic effect on reducing proteinuria levels. As such, the

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claims of the instant application are not obvious over claims 1-5 of the '906 patent in view of London and/or Vukicevic.

Finally, applicants respectfully submit that the issuance of the amended claims of the instant application would not provide an unjustified extension of the term of the right to exclude granted by the '906 patent. Accordingly, applicants request that the Examiner withdraw this obviousness-type double patenting rejection.

U.S. Application No. 10/816,768, London and Vukicevic
Claims 56, 71-76 and 78

The Examiner has provisionally rejected claims 56, 71-76 and 78 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 10 and 16-18 of co-pending U.S. Application No. 10/816,768 ("the '768 application") in view of London and further in view of Vukicevic. Applicants traverse.

First, applicants have canceled claims 72-75, thus rendering the Examiner's rejection moot with respect to these claims.

Second, with respect to the remaining claims, claims 10 and 16-18¹ of the '768 application cannot form the basis for an obviousness-type double patenting rejection for the same reasons that claims 1-13 of the '432 patent and claims 1-5 of the '906 patent cannot form the basis for an obviousness-type double patenting rejection.

Withdrawn claims 10 and 16-18 of the '768 application are directed to TGF- β family protein mutants having a leader sequence domain operatively linked to the C-terminal domain of the TGF- β family member protein. Claims 10 and 16-18 of the '768 application do not recite OP-1 and/or morphogens comprising the C-terminal seven cysteine domain as suggested by the Examiner. And, as acknowledged by the Examiner, claims 10 and 16-18 of the '768 application do not recite treatment of renal diseases.

The amended claims of the instant application recite specific BMPs, not TGF- β family protein mutants having a leader sequence domain operatively linked to the C-terminal domain of the TGF- β family protein mutant. A combination of claims 10 and 16-18 of '768 application with London and/or Vukicevic would yield a

¹Applicants note that claims 10 and 16-18 of the '768 application are currently withdrawn.

combination of a TGF- β family protein mutant having a leader sequence domain operatively linked to the C-terminal domain of the TGF- β family protein mutant, with an ACE inhibitor. The amended claims of the instant application do not recite such a combination. Therefore, the amended claims of the instant application are patentably distinct from claims 10 and 16-18 of the '768 application.

Moreover, applicants submit that the synergistic effect on reducing proteinuria levels using the combination of an ACE inhibitor with specific BMPs, as recited in the amended claims of the instant application, is nowhere taught or suggested by claims 10 and 16-18 of the '768 application, either alone or in combination with London and/or Vukicevic.

Finally, applicants respectfully submit that the issuance of the amended claims of the instant application would not provide an unjustified extension of the term of the right to exclude granted by the '768 application. Accordingly, applicants request that the Examiner withdraw this provisional obviousness-type double patenting rejection.

U.S. Patent No. 6,677,432, London, Vukicevic and Salvetti
Claims 56 and 69

The Examiner has rejected claims 56 and 69 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of the '432 patent in view of London and further in view of Vukicevic and Salvetti.

As discussed above, claims 1-13 of the '432 patent, either alone or in combination with London and/or Vukicevic, cannot form the basis for an obviousness-type double patenting rejection. Salvetti does not remedy this deficiency. Salvetti discloses ACE inhibitors and that enalapril is more potent than other ACE inhibitors and has a longer duration of action. At best, the combination of claims 1-13 of the '432 patent with London, Vukicevic and/or Salvetti would yield a combination of the specific OP-1 mutant of the '432 patent with enalapril as the ACE inhibitor. The claims of the instant application do not recite such a combination.

Moreover, claims 1-13 of the '432 patent, either alone or in combination with London, Vukicevic and/or Salvetti do not teach or suggest that the combination of an ACE inhibitor with the specifically recited BMPs would have a synergistic effect on

reducing proteinuria levels, as recited in the amended claims of the instant application.

For the same reasons discussed above for claims 56, 71-76 and 78, applicants request that the Examiner withdraw this obviousness-type double patenting rejection.

*U.S. Patent No. 6,846,906, London, Vukicevic and Salvetti
Claims 56 and 69*

The Examiner has rejected claims 56 and 69 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-5 of the '906 patent in view of London and further in view of Vukicevic and Salvetti.

As discussed above, claims 1-5 of the '906 patent, either alone or in combination with London and/or Vukicevic, cannot form the basis for an obviousness-type double patenting rejection. Furthermore, Salvetti does not remedy this deficiency. At best, the combination of claims 1-5 of the '906 patent with London, Vukicevic and/or Salvetti would yield a combination of a chimeric TGF- β superfamily protein with enalapril. The claims of the instant application do not recite such a combination.

Moreover, claims 1-5 of the '906 patent, either alone or in combination with London, Vukicevic and/or Salvetti do not teach

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or suggest that the combination of an ACE inhibitor with the specifically recited BMPs would have a synergistic effect on reducing proteinuria levels, as recited in the amended claims of the instant application.

For the same reasons discussed above for claims 56, 71-76 and 78, applicants request that the Examiner withdraw this obviousness-type double patenting rejection.

*U.S. Application No. 10/816,768, London, Vukicevic and Salvetti
Claims 56 and 69*

The Examiner has provisionally rejected claims 56 and 69 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 10 and 16-18 of the '768 application in view of London and further in view of Vukicevic and Salvetti.

As discussed above, claims 10 and 16-18² of the '768 application, either alone or in combination with London and/or Vukicevic, cannot form the basis for an obviousness-type double patenting rejection. Salvetti does not remedy this deficiency. At best, the combination of claims 10 and 16-18 of the '768 application with London, Vukicevic and/or Salvetti would yield a

² Applicants note that claims 10 and 16-18 of the '768 application are currently withdrawn.

combination of a TGF- β family protein mutant having a leader sequence domain operatively linked to the C-terminal domain of the TGF- β family protein mutant with enalapril. The claims of the instant application do not recite such a combination.

Moreover, claims 10 and 16-18 of the '768 application, either alone or in combination with London, Vukicevic and/or Salveti do not teach or suggest that the combination of an ACE inhibitor with the specifically recited BMPs would have a synergistic effect on reducing proteinuria levels, as recited in the amended claims of the instant application.

For the same reasons discussed above for claims 56, 71-76 and 78, applicants request that the Examiner withdraw this provisional obviousness-type double patenting rejection.

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CONCLUSION

In view of the foregoing amendments and remarks, applicants request that the Examiner reconsider and withdraw all outstanding rejections and allow the pending claims.

The Examiner is invited to telephone applicants' representatives regarding any matter that may be handled by telephone to expedite allowance of the pending claims.

Respectfully submitted,



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